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3. The Formula of Morphine. By R. B. Dott, F.I.C., and Ralph Stockman, M.D.

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As the alkaloid morphine, discovered in 1804, was the first substance of the kind known, it naturally received a good deal of attention. Some years later the new base was analysed by several distinguished chemists, but their results did not lead them to a formula accurately indicating the composition of the alkaloid. To Laurent* belongs the honour of having given the formula $C_{17}H_{19}NO_3$ (using the modern notation), the accuracy of which formula has been confirmed by subsequent analyses, particularly by those of Matthiessen and Wright.† Nothing was ever observed to suggest that the formula is a multiple of these members until Wright, after an elaborate investigation of the derivatives of morphine and codeine, came to the conclusion that the true formula must be at least double the empirical, and that we ought therefore to write $C_{34}H_{38}N_2O_6$. The reasons which led Dr Wright to that conclusion are, briefly stated, as follows :—

It was found that when morphine is heated with hydrochloric acid in a sealed tube,‡ there is produced, besides apomorphine, a mixture of amorphous bases. This mixture, when fractionated, appears by analysis to contain a base "R" ($C_{34}H_{36}Cl_2N_2O_4$) homologous with chlorocodide, and also a base "P" ($C_{34}H_{39}ClN_2O_6$). Now it is evident that if it were clearly established that the latter base contains only 1 atom of Cl to the 34 of C, and if at the same time it were proved that no polymerisation had taken place in its formation, the formula of morphine must be $C_{34}H_{38}N_2O_6$, and not $C_{17}H_{19}NO_3$. Similarly, chlorocodide is apparently preceded in its formation by a base homologous with base "P ;" and as chlorocodide yields codeine by the simple action of water, it is manifest that no polymerisation has taken place. The formula of codeine must therefore be $C_{36}H_{42}N_2O_6$; and as codeine is simply the methyl ether

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* *Ann. Ch. Phy.*, lxii. 96.

† *Proc. Roy. Soc.*, xvii. 455.

‡ *Proc. Roy. Soc.*, xvii. 460: xviii. 83.

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of morphine, it follows that morphine must be $C_{34}H_{38}N_2O_6$. The other argument for the higher formula is deduced from a study of the acetyl derivatives of morphine. In the course of an extended investigation of these bodies,* Wright obtained what he describes as monoacetylmorphine [$C_{34}H_{37}(C_2H_3O)N_2O_6$]. If we were certain that a derivative of that composition had been formed, and that its formation was unaccompanied by polymerisation, the proof for the higher formula would be complete.

In preparing certain of the morphine derivatives for the purposes of pharmacological investigation, we have obtained results which lead us to a different conclusion regarding the formula from that arrived at by Wright, and our experiments are therefore described in the present paper.

(1) *Chlorocodide.*—This substance was prepared exactly in the manner described by Matthiessen and Wright. Although white or nearly so when freshly precipitated, it became of a pale green colour on exposure to the air. The chloroplatinate dried at 120°, yielded on ignition 18·43 per cent. Pt. Wright obtained 18·60 per cent. Pt. The percentage required by the formula $C_{36}H_{40}Cl_2N_2O_4.PtH_2Cl_6$, is 18·81. On uniting the first and third fractions obtained in purifying the base, the mixture gave a chloroplatinate which yielded 17·97 per cent. Pt. As regards physiological action, the second fraction nearly resembled apomorphine, while the mixed fractions rather approached codeine in its action on animals. The fact that the so-called chlorocodide and its hydrochloride are non-crystalline, shows that it is something other than a mixture of apomorphine and codeine, and that conclusion is confirmed by the analytical results. These results, however, indicate that chlorocodide is not obtained in the pure state by the authorised process, and that the substance is probably a mixture of bases, most likely of a chlorinated and non-chlorinated base. Indeed, it is very difficult to derive any definite information from an amorphous mixture, such as that produced by the action of hydrochloric acid on morphine or codeine. There is really no evidence to prove that a compound containing 1 atom of chlorine to 34 atoms of carbon has been formed from morphine, or that a similar product has been obtained from codeine.

(2) *Acetylmorphine.*—Wright describes four acetyl derivatives

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* *Jour. Chem. Soc.*, [2], xii. 1031.

as obtained by him from morphine. At present we are only concerned with the monoacetyl compound, represented by the formula $C_{34}H_{37}(C_2H_3O)N_2O_6$. It was prepared by the action of acetic anhydride on morphine, "when a considerably smaller quantity" of the anyhdride is taken than is required to form diacetylmorphine. The product "resembles β-diacetylmorphine in every particular, save that it yields different numbers on analysis." The numbers given by Wright agree only fairly well with theory. "That the substance is truly a monoacetyl morphine, and not a mixture of morphine and diacetyl derivatives, is shown by the fact that the base itself is soluble in ether; whereas morphine is practically not soluble in that menstruum. Moreover, a mixture of β-diacetylmorphine hydrochloride and morphine hydrochloride in equal quantities dissolved in a little water, allows almost the whole of the latter salt to crystallise out, and does not dry up to a varnish over sulphuric acid, but to a crystalline mass wetted by a syrup, which finally dries up to a glaze over the crystals." Wright obtained from the chloroplatinate 19·45 per cent. Pt; the monoacetylmorphine compound requiring 19·29 per cent. of metal.

We have repeated Wright's experiments, with the results undernoted. 15 grams of morphine were dried at 120° C., and thoroughly mixed with 1·25 gram acetic anhydride. The mixture was then warmed on the water-bath for half an hour, treated with water and with sodium carbonate in slight excess, and the whole shaken up with ether. On separating and evaporating the ether a non-crystalline residue remained, to which dilute hydrochloric acid was added in quantity just sufficient to render faintly acid. The strong solution showed no signs of crystallisation even after the lapse of two days. To a portion of the solution platinic chloride was added, and the washed precipitate dried at 120° C. On ignition 0·124 gram gave 0·023 gram Pt = a yield of 18·54 per cent.

$C_{34}H_{36}(C_2H_3O)_2N_2O_6.PtH_2Cl_6$ gives 18·48 per cent. Pt.
$C_{34}H_{37}(C_2H_3O)N_2O_6.PtH_2Cl_6$ gives 19·53 per cent. Pt.

In this experiment there is no evidence that any monoacetylmorphine was formed, although the conditions were most favourable for its formation. The solution must have contained either diacetylmorphine or a mixture of tetracetylmorphine and morphine. Wright's assumption, that the supposed monoacetylmorphine could not have contained morphine, because the latter is insoluble in ether, is not well founded. Under certain conditions, probably when it is freshly precipitated and partially amorphous, morphine is soluble in ether. The evidence from the non-crystalline condition of the product is far from conclusive, as crystallisation is influenced by a variety of circumstances not well understood; and it must be remembered that tetracetylmorphine hydrochloride is a very soluble and not readily crystallisable salt, which may form a basic compound with morphine.

(3) *Ethylmorphine.*—Since Wright contributed his papers on morphine derivatives, it has been shown by Grimaux,* that part of the hydrogen in the morphine molecule may be replaced by alcohol radicals. We endeavoured to prepare a monoethyl derivative [$C_{34}H_{37}(C_2H_5)N_2O_6$], by heating together equivalent quantities of morphine, soda, and ethyl iodide, in alcoholic solution. The alcohol having been evaporated, the residue was exhausted with chloroform, and the chloroform extract converted into hydrochloride. The resulting crystalline mass was pressed in calico, and a chloroplatinate prepared from the crystals. Dried at 130°, 0·44 gram gave on ignition 0·083 gram = 18·86 per cent. Pt; 0·2965 gram gave 0·056 gram Pt = 18·88 per cent. Pt. The expressed mother-waters from the crystals yielded a platinum salt, which gave on ignition—

0·3239 gram = 0·061 gram Pt = 18·83 per cent.
Mean of three determinations = 18·85 per cent. Pt.
$C_{34}H_{36}(C_2H_5)_2NO_6 \cdot PtH_2Cl_6$ = 18·97 per cent. Pt.
$C_{34}H_{37}(C_2H_5)N_2O_6 \cdot PtH_2Cl_6$ = 19·50 per cent. Pt.

Whence it is manifest that under the conditions described, only diethylmorphine is formed (using the nomenclature adopted by Wright). In fine, there does not appear to be any evidence to justify the adoption of a higher formula for morphine than the empirical ($C_{17}H_{19}NO_3$), which is the formula still in general use. It follows that Wright's "diacetylmorphine" should be named *acetylmorphine*, and his "tetracetylmorphine" *diacetylmorphine.*

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* *Comptes Rend.*, xcii.